

Early inflammatory changes in perimenopause: A risk for neurodegeneration



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Abstract

Perimenopause is a natural transition into menopause which is often characterized through fluctuating estrogen levels, and associated with age-related increase in the risks of neurodegenerative diseases. A decline in estrogen hormone levels disrupts immune regulation and leads to impaired neuroinflammation and mitochondrial function, which eventually results in poor cognitive function. Estrogen receptor ER- β seems to play a neuroprotective role in modulating inflammation and oxidative stress. However, reduced activation during perimenopause promotes neurodegeneration. Hormone Replacement Therapy (HRT) is primarily employed to ameliorate menopausal symptoms and enhance cognitive function. However, it bears potential risks, including augmenting the risk of cardiovascular disease and cancers. Dietary interventions and antioxidants exhibits neuroprotective potential and supporting the pharmacological strategy of inflammation management. Regular physical activities and stress management contribute to countering systemic inflammation with effective brain health. Hence, an integrated approach incorporating hormonal balance, lifestyle changes, and targeted therapy toward neuroinflammation is critical to enhancing women's long-term health outcome. Understanding the mechanisms of neurodegenerative processes induced by perimenopause can create a valuable basis for producing effective interventions to manage cognitive function and overall health in peri-and post-menopausal women. This review emphasizes the significance of addressing systemic inflammation in perimenopause to improve health and quality of life for women.

Keywords: Perimenopause; Systemic inflammation; Estrogen regulation and Neurodegeneration.

1. Introduction

Menopause is the process of variable hormonal regimes leading to disturbed cycles and ultimately complete cessation of menstruation for at least one year. This transition may impair ovarian function because of a decrease in estrogen and progesterone levels. Hormonal imbalance causes several signs and symptoms, including mood changes, hot flashes, sleep disturbances, and increased systemic inflammation. The understanding of this transitional phase helps significantly to determine healthcare interventions to control the symptom and prevent the long-term health risks (1). Alteration of hormone in perimenopause trigger natural biological transitions that produce significant influences on manifold body systems. Moreover, various studies reveal that decreasing

estrogen levels may produce inflammatory conditions that leads a woman's risks for Alzheimer's disease (AD), Parkinson's disease (PD), and vascular dementia (VD) (2). The determination of this connection is essential for effective prevention of interventions. The maximum women characteristically experience perimenopause between the age of 40 and 50. As per the epidemiological research findings the prevalence of perimenopausal symptoms influences about 80% of women, but variations may be occurred due to genetic, life-style and environmental factors (3). The estrogen-regulated pathways may be impaired due to decreasing level of estrogen during the phase of the reproductive years, mainly that associated with neuroprotection, immune modulation and mitochondrial function (4). Estrogen is a regulatory hormone, acts via estrogen receptor (ER) subtypes, alpha (ER- α) and beta (ER- β). Mainly, ER- β provide a pivotal role in controlling neuroinflammatory processes by regulating the inflammasome, i.e. a prime component of the innate immune response (5). As the level of estrogen declines, this regulation is reduced, which causes to increased neuroinflammation, mitochondrial dysfunction and oxidative stress that led to neuronal damage and impair the cognitive function (6). This review exhibits that after perimenopause, a systemic inflammatory condition occurs, and acts as risk factors for neurodegenerative disease (ND) (7).

2. Menopausal transition and associated disorders

The decreasing the estrogen level during menopause transition, significantly alter the various physiological activities and also increase the risk of chronic disease progression. The most common health issue is cardiovascular disorder, as estrogen helps in maintain the cholesterol level that promote vasodilation and reduced the oxidative stress. The deficiency of estrogen leads to higher level of low-density cholesterol, atherosclerosis, and increases the risk of hypertension, and heart disease (8,9). Moreover, the estrogen plays a prime role in inhibiting the bone resorption, therefore, during the menopause, its decreases and accelerates bone loss. This also decrease the bone mineral density and increases the risk of osteoporosis and fractures, particularly in the wrist, spine and hips (10). Metabolic variations may be occurred and many women facing increased visceral fat accumulation, dyslipidemia and insulin resistance. It may also be contributing to metabolic syndrome and a higher risk of developing type 2 diabetes (11). Additionally, decreasing level of estrogen may triggers chronic inflammation, which can lead to autoimmune conditions like rheumatoid arthritis and osteoarthritis (12). These inflammatory responses may be extended to the brain, enhancing the risk of cognitive decline and NDs like AD (13). In addition, most women report mood swings, depressions, anxiety, and insomnia, affecting their cognitive and emotional well-being (14).

Most of the abovementioned risks need to be reduced by different preventive measures. Exercise, lifestyle modification through weight reduction, and smoking cessation can be effective for the improvement of general health. Nutritional support in the form of calcium, omega-3 fatty acids, vitamin D, and phytoestrogens helps maintain bone and cardiovascular health (15). In some cases, hormone replacement therapy (HRT) could be supported to improve severe symptoms and prevent long-term complication. Additionally, regular health checks such as bone density examinations, blood glucose analysis, cardiovascular screening, could assure early detection and management of health risks, thereby enhancing the overall health outcomes for the menopause women (16).

3. Potential therapeutic interventions

3.1. Hormone replacement therapy (HRT)

HRT majorly with the use of estrogen can be looked upon widely for its neuroprotective potentials in postmenopausal women. Estrogen is known to influence cognition, reduce oxidative stress, and increase synaptic plasticity, thus possibly acting to reduce the risk of neurodegenerative disorders. Several studies suggest that estrogen regulates neurotransmitter action, enhances blood flow to the brain, and possesses properties that combat inflammation, these mechanisms contribute to brain health (16).

Apart from these benefits, HRT is associated with some side effects, such as an increased risk of stroke, venous thromboembolism, and certain cancers, which may inhibit its prevalent clinical application. The risk-benefit ratio may be depended on the factors such as the characteristics of individual patients,

duration of therapy and onset timing etc. Early initiation of HRT, mainly in the "critical window" hypothesis, leads that therapy starting earlier to menopause may give significant cognitive effects while reducing risks (16). Furthermore, studies are required to optimize HRT procedures, ensuring maximal neuroprotection while mitigating adverse effects.

3.2. Nutritional interventions for hormonal and neurological health

Nutritional interventions exhibit a prime role in maintaining hormonal balance, to reduce inflammation, and promote neuroprotection, predominantly in postmenopausal women undergoing HRT. As level of estrogen levels decreases with menopause, women suffer an increased risk of cognitive impairment, ND, and metabolic disturbances. A balanced diet, rich in minerals, vitamins, fats, antioxidants, carbohydrates, and protein nutrients, can serve as a complementary approach to mitigate these risks and enhance the benefits of HRT.

3.3. Phytoestrogens: Natural estrogen modulators

Plant-derived compound having estrogen-like activity is known as phytoestrogen, mainly present in soy products-isoflavones, flaxseeds, quercetin, naringenin, and legumes etc. These compounds may be attached to estrogen receptors and provide mild estrogenic effects, significantly improving menopausal symptoms and supporting cognitive activity. Epidemiological findings suggested that individuals consuming high amounts of soy-based foods, have a lower occurrence of menopausal symptoms and NDs. Though, the efficacy of phytoestrogens differs among individuals, depending on gut microbiota composition and metabolic activity (17).

3.4. Omega-3 fatty acids: protecting brain function

Long-chain omega-3 fatty acids, including eicosatetraenoic acid (EPA) and docosahexaenoic acid (DHA), play a critical role in brain health by reducing inflammation, enhancing synaptic plasticity, and supporting neuronal membrane integrity. These essential fatty acids, found in fatty fish (salmon, mackerel, sardines), flaxseeds, and walnuts, are particularly beneficial for postmenopausal women, as they counteract estrogen-related neuroinflammation and oxidative stress. Clinical studies indicate that omega-3 supplementation may reduce the risk of cognitive decline and improve mood regulation, which is crucial in menopause (18).

3.5. Antioxidants and polyphenols: Combating oxidative stress

Oxidative stress and chronic inflammation are key contributors to neurodegeneration and hormonal imbalances. Antioxidant-rich foods, such as green leafy vegetables (spinach, kale), berries, turmeric, and dark chocolate, provide polyphenols, flavonoids, and vitamins C and E, which neutralize free radicals and support mitochondrial function. Curcumin, the active compound in turmeric, has demonstrated neuroprotective effects by reducing beta-amyloid plaques associated with Alzheimer's disease. Incorporating these foods into daily diets can enhance the neuroprotective effects of HRT (19).

3.6. B Vitamins and magnesium: Supporting neurotransmitter function

Vitamins B, particularly B6, B9 (folate), and B12, play essential roles in neurotransmitter synthesis and homocysteine metabolism. Elevated homocysteine levels are linked to cognitive impairment and an increased risk of neurodegenerative diseases. Green leafy vegetables, whole grains, eggs, and dairy products provide an adequate supply of these essential vitamins. Similarly, magnesium, found in nuts, seeds, and legumes, supports brain plasticity, reduces stress, and helps regulate estrogen metabolism, making it crucial for menopausal health (20).

3.7. Vitamin D and Calcium: Hormonal and bone health

Vitamin D is essential for calcium absorption, immune regulation, and brain health. Estrogen plays important role in metabolism of vitamin D, and postmenopausal women exerts high risk of both vitamin D deficiency and osteoporosis. Exposure of sun light, curd, milk fortified dairy products, vitamin, minerals and food supplements can help maintain ideal levels, supporting both neurological and skeletal health of menopausal women (21).

3.8. Exercise and stress management

Lifestyle changes such as regular exercise, yoga, meditation and stress management are vital that may help to significantly reduce inflammation and support cognitive health. Regular physical activities, particularly aerobic exercises, have been revealed to minimize systemic inflammation by regulating immune responses and reducing the production of inflammatory cytokines. Moreover, workout promotes neuroplasticity by alleviating levels of brain-derived neurotrophic factor. It is a protein used vital for neuron growth, and helps to enhance neurogenesis in the hippocampus that improve the memory and learning (22). Muscle training also helps to lowering chronic inflammation and maintain muscle mass. Additionally, chronic stress increases cortisol levels, when it occurs for long period, can lead to inflammation and cognitive decline. Stress management therapy, such as meditation, reduce cortisol levels and exerts lower inflammatory responses like C-reactive protein (CRP) and interleukin-6 (IL-6), and helps to protecting against physical and mental health challenges. Also, these therapies improve cognitive function, enhance concentration, and boost memory and also giving a protective effect against stress-related cognitive impairment (23).

4. Conclusion

Perimenopause signifies a critical phase in women's health, mainly for brain function and overall neurological health. In this phase, the body experiences significant hormonal changes that can directly impact on cognitive health. The most significant factors are systemic inflammation which influenced the NDs, is a regulating risk that can be addressed through targeted interventions. To determining inflammation as a significant factor to long-term neurological decline, it becomes essential to prioritize research into personalized strategies for reducing this risk. Advancing these approaches will not only empower women to manage their health proactively during perimenopause but also help mitigate the long-term neurological consequences associated with this transformative life stage.

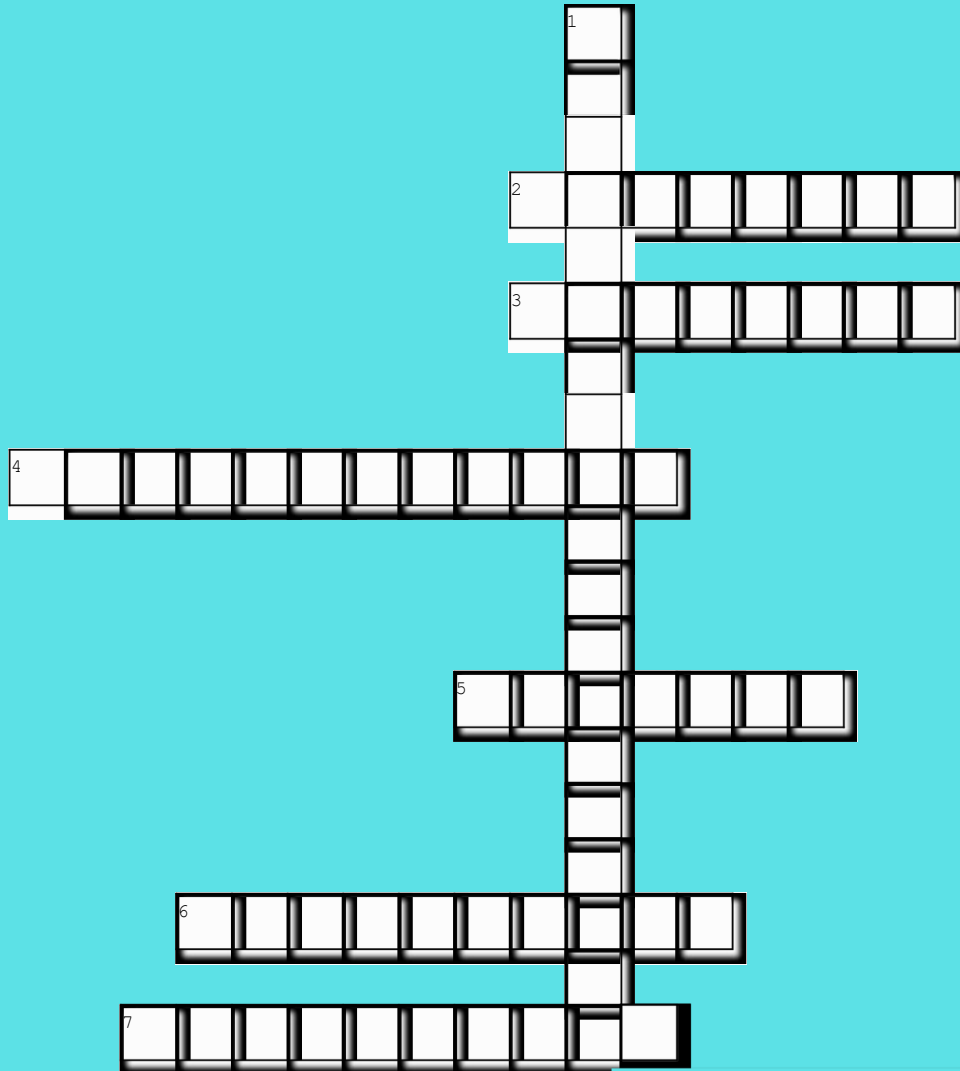
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Symptoms of Perimenopause and Menopause

Complete the crossword puzzle below



Across

Sleep problems
Feeling mentally unclear
Sensation of rapid or irregular heartbeat
Mental and physical exhaustion
Fluctuations in mood
Sudden feelings of intense warmth

Down

1. Feeling mentally unclear

Answers are on page no: 81